

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

Conservation
et Corporations Canada
Bureau des brevets
Ottawa, Canada
K1A 0Z9

Conservation et
Corporations Canada
Patent Office

(11) (C) 1,315,689
(21) 548,964
(22) 1987/10/09
(45) 1993/04/06
(52) 167-245

(51) INTL. CL. 5 A61K-31/485

(19) (CA) CANADIAN PATENT (12)

(54) Quarternary Derivatives of Noroxymorphone which Relieve
Nausea and Emesis

(72) Goldberg, Leon I. , U.S.A.

(73) University of Chicago , U.S.A.

(30) (US) U.S.A. 092,470 1987/09/03

(57) 19 Claims

NO DRAWING

Canada

DC: 6224 (10/8) 41

1315689

40355-49

. 1 -

CONTRARY DERIVATIVES OF NORDYMORPHONE
WHICH RELIEVE NAUSEA AND EMESIS

5 The administration of therapeutic doses of morphine and other clinically useful narcotic analgesics is often accompanied by unpleasant side effects on the gastro-intestinal system. For instance, morphine and related opiates such as meperidine and methadone may retard
 10 intestinal mobility by causing contractions of the small bowel circular smooth muscle.

Morphine and related narcotics may also induce nausea and increased mobility of the gastro-intestinal tract
 15 resulting in nausea or vomiting. These side effects are caused by direct stimulation of the chemoreceptor trigger zone for emesis in the area postrema of the medulla. (Goodman and Gilman, The Pharmacological Basis of Therapeutics, p. 502 (6th ed. 1900)). Studies have shown that morphine and other
 20 narcotics cause emesis in dogs. For example, Wang and Glaviano, JET 111:329-334 (9143), reported that administration of 0.5 mg/kg of morphine intravenously to 12 dogs resulted in emesis in 9 dogs within an average of 2.4 minutes. (mg/kg refers to milligrams of morphine per
 25 kilograms of body weight.) When 1.0 mg/kg of



A

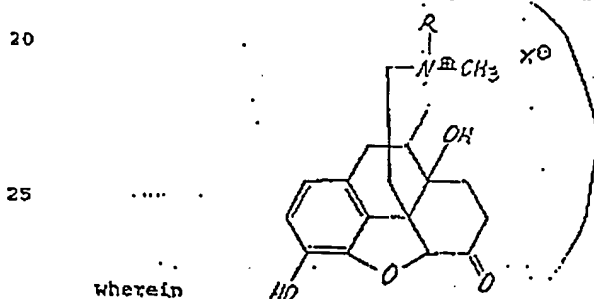
1315689

-2-

1 morphine was administered intramuscularly to 13 dogs, 12
of them vomited within an average time of 3.5 minutes.

5 U. S. Patent No. 4,176,186 to myself and others
disclosed treatment of intestinal immobility associated
with the use of narcotic analgesics through the
administration of quaternary derivatives of
10 noroxymorphone. It has now been discovered that the
same compounds are also useful for the treatment, both
prophylactic and therapeutic, of the nausea and vomiting
associated with the administration of these drugs.

15 According to the invention, therefore, nausea and
vomiting by warm-blooded animals receiving morphine and
related opiates, meperidine, methadone or the like, may
be prevented or relieved by the administration of
methylnaltrexone or other quaternary derivatives of
noroxymorphone represented by the formula:



wherein

30 R is allyl or a related radical such as
chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, especially a chloride,
bromide, iodide or methylsulfate anion.

35 These compounds are administered to the animal
either prior to or simultaneously with the
administration of the narcotic analgesic. They may be

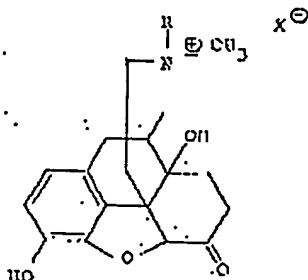
1315689

- 3 -

administered either enterally or parenterally. There has not been observed any interference with the analgesic activity of the opiate.

As used herein, unless the sense of the usage indicates otherwise, the term "morphine" refers to any narcotic analgesic.

This invention relates to the use of quaternary derivatives of noroxymorphone to prevent or relieve nausea and vomiting associated with the administration of morphine to warm-blooded animals. The useful compounds are represented by the formula:



wherein

R is allyl or a related radical such as chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, especially a chloride, bromide, iodide or methylsulfate anion.

The compounds are synthesized as described in United States Patent No. 4,176,186. A particularly preferred noroxymorphone derivative is methylnaltrexone, but other compounds represented by the above formula are also suitable.

Methylnaltrexone or other noroxymorphone derivatives may be administered to the patient either

1315689

-4-

1 enterally or parenterally. However, a preferred method
of administration is by injection. Nausea and emesis
may follow after even a single dose of morphine, unlike
5 intestinal immobility which is usually the effect of
chronic repeated usage of the drug. Consequently, it is
contemplated that the patient will be given an injection
of methylnaltrexone prior to surgery or other occasion
when morphine is used to treat acute pain.

As illustrated by the following Controls and
10 Examples, our studies show that methylnaltrexone
inhibits emesis when administered either together with
the morphine or before the morphine is administered. It
is thought that methylnaltrexone or other quaternary
noroxymorphone derivatives may be administered up to two
15 hours before the administration of morphine, but that
period may be variable. In our studies,
methylnaltrexone was administered intramuscularly by
means of a syringe. Methylnaltrexone may also be
administered enterally or parenterally by other means.
20 It has been found to be effective in dosages in the
range of about 0.05 mg/kg to about 1.0 mg/kg for each 1
mg/kg of administered morphine. It was found effective
when administered in the same syringe as morphine and
also when administered up to about one hour before the
25 administration of morphine.

The effect of methylnaltrexone in reversing the
emetic effects of morphine is illustrated herein. The
unit of mg/kg refers to milligrams of substance
administered per kilograms of body weight.

30
CONTROL 1 AND EXAMPLE 1

One mg/kg of morphine was administered
intramuscularly to five dogs. Four dogs vomited. In
each instance, vomiting occurred within four minutes.
35 On a different day the same dose of morphine was

1315689

-5-

1 administered intramuscularly to the same five dogs in
the same syringe with 1 mg/kg of methylnaltrexone. None
of the dogs vomited.

5 CONTROL 2 AND EXAMPLE 2

Six dogs were given intramuscular doses of 1 mg/kg
of morphine. All six dogs vomited. On an additional
day the same dose of morphine was combined with 0.5
mg/kg of methylnaltrexone and administered in the same
10 syringe to the same dogs. None of the dogs vomited.

CONTROL 3 AND EXAMPLE 3

One mg/kg of morphine was administered
intramuscularly to three dogs. All three dogs vomited.
15 On an additional day the morphine was combined with 0.25
mg/kg of methylnaltrexone and administered in the same
syringe. None of the dogs vomited.

CONTROL 4 AND EXAMPLE 4

20 Methylnaltrexone was administered to two dogs prior
to the administration of 1 mg/kg morphine. In one dog,
0.5 mg/kg of methylnaltrexone was administered
intramuscularly 15 minutes before the morphine. No
vomiting occurred. In the second dog, the same dose of
25 methylnaltrexone was administered 30 minutes before the
administration of morphine. No vomiting occurred.

CONTROL 5 AND EXAMPLE 5

0.05 mg/kg methylnaltrexone was administered
30 intravenously to four dogs one minute prior to the
administration of 1.0 mg/kg morphine. No vomiting
occurred in any of the dogs. On a different day, the
same animals were given 1.0 mg/kg morphine without the
administration of methylnaltrexone. All four dogs
35 vomited.

1315689

- 6 -

The administration of methylnaltrexone alone was found to produce no noticeable effects in the animals. Previous studies with larger doses of methylnaltrexone have

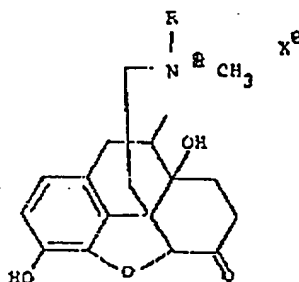
- 5 demonstrated that unlike the non-quaternary naltrexone, methylnaltrexone does not precipitate withdrawal systems in morphine-tolerant dogs. Russell et al., Eur. J. Pharmacol. 78:255-261 (1982). Methylnaltrexone has not been found to interfere with the analgesic activity of morphine or
- 10 narcotics.

A?

40.255-99

၁။ ခရစ်ယာန် ဂိုဏ်းတို့၏ အကျဉ်းချုပ်

.C



R is allyl or a related radical; and
X is the anion of an acid;

2. Use as claimed in claim 1 in which R is chloroalkyl, cyclopropyl-methyl or propargyl.

4. Use as claimed in claim 1, where the compound is in an amount between 0.05 mg/kg and about 1.0mg/kg of animal body weight.

20 5. Use as claimed in claim 1, as an enteral-
ly administered compound;

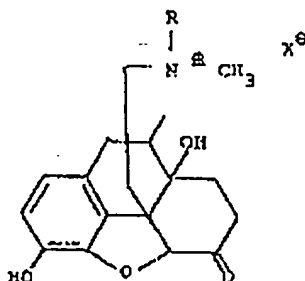
-B- 1315689

5. Use as claimed in claim 1, as parenterally administered compound.
- 5 7. Use as claimed in claim 6, as an injectably administered compound.
8. Use as claimed in claim 1, prior to the administration of the narcotic analgesic.
9. Use as claimed in claim 1, up to about two hours prior to the administration of the narcotic analgesic.
- 10 10. Use as claimed in claim 1, concurrently with the administration of the narcotic analgesic.
11. Use of methylnaltrexone to prevent or relieve nausea and emesis associated with the use of a narcotic analgesic in war-blooded animals.
- 15 12. Use as claimed in claim 11 in an amount of between 0.05 mg/kg of animal body weight and about 1.0 mg/kg of animal body weight simultaneously with or up to about two hours prior to the time of administration of the narcotic analgesic.
- 20 13. Use as claimed in claim 12, as a parenterally administered compound.

-80-

1315689

14. A pharmaceutical composition for preventing or relieving nausea and emesis comprising a narcotic analgesic in combination with at least one quaternary derivative of noroxymorphone:



wherein

R is allyl or a related radical; and

X is the anion of an acid;

- and wherein the quaternary derivative of noroxymorphone is present in an amount effective to prevent or relieve nausea induced by the narcotic analgesic.

15. A pharmaceutical composition as claimed in claim 12 in which R is chloroallyl, cyclopropyl-methyl or propargyl.

16. A composition as claimed in claim 12 in which X is a chloride, bromide, iodide or methanesulfate anion.

17. A composition according to claim 14, wherein the quaternary derivative of noroxymorphone is present in a unit dose of between about 0.05 mg and about 1.0 mg for each 1 mg of morphine.

18. A composition as claimed in claim 14, wherein the narcotic analgesic is morphine.

1315689

-8b-

19. A composition as claimed in claim 14, wherein the
quaternary derivative of nortoxymorphone is
methylnaltrexone.



-9-

1 QUATERNARY DERIVATIVES OF NOROXYMORPHONE
 WHICH RELIEVE NAUSEA AND EMESIS

5 ABSTRACT OF THE DISCLOSURE

 Quaternary derivatives of noroxymorphone are used
to prevent or relieve nausea and emesis associated with
the use of narcotic analgesics without interfering with
the analgesic activity of the drugs. A particularly
10 preferred compound is methylnaltrexone. The compound is
administered in a concentration between 0.05 mg/kg and
1.0 mg/kg prior to or concurrently with the
administration of the narcotic analgesic.

SUBSTITUTE
REPLACEMENT

SECTION is not Present

Cette Section est Absente